DIFFERENTIATING THE ROLES OF THE CEREBELLUM AND MOTOR CORTICES DURING VISUOMOTOR ADAPTATION USING EITHER HAND OR WHOLE ARM REACHING MOVEMENTS

By

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MASTERS BY RESEARCH

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Abstract

The control of proximal versus distal upper limb movements are believed to be subserved by somewhat distinct neural pathways. Direct connections from the primary motor cortex (M1) to distal muscles supports the key role of M1 in the production and control of hand/finger movements, whereas impaired reach behaviour after cerebellar lesions and ataxia point to the cerebellum as a vital neural substrate contributing to whole arm reaching. However, no study has sought to directly elucidate the roles of both the cerebellum and M1 during specific motor tasks using either movements of the hand and fingers or the whole arm. Here, young healthy participants received anodal transcranial direct current stimulation (TDCS) over the lateral cerebellum, M1 or sham stimulation during a visuomotor rotation task requiring either hand/finger movements or whole arm reaching movements. It was found that cerebellar TDCS enhanced adaptation for participants completing the Arm task as they displayed significantly reduced error at the end of task compared to the M1 or sham group. Conversely, M1 stimulation resulted in improved adaptation performance during the Hand task compared to cerebellar or sham groups. This effect on adaptation did not persist after a 50 minute break (40 minutes without stimulation), when re-tested on the same task. These results demonstrate an effector specific effect of TDCS over M1 and the cerebellum during visuomotor adaptation and could prove important to the use of TDCS as a viable clinical tool in the treatment of upper limb motor deficits moving forward.

Keywords: *Motor Adaptation, Cerebellum, Primary Motor Cortex, Transcranial Direct Current Stimulation*

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Abbreviations

CBI	Cerebello-brain Inhibition
CCW	Counter-clockwise
CM	Cortico-motorneuronal
DCN	Deep Cerebellar Nuclei
GABA	Gamma-aminobutyric Acid
LTD	Long-term Depression
LTP	Long-term Potentiation
M1	Primary Motor Cortex
MEP	Motor Evoked Potential
MRS	Magnetic Resonance Spectroscopy
NMDA	N-methyl-D-aspartate
PD	Parkinson's Disease
RN	Red Nucleus
SCI	Spinal Cord Injury
TDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
VAS	Visual Analogue Scale
vBOT	Robotic Manipulandum
VMA1	Visuomotor Adaptation Phase One
VMA2	Visuomotor Adaptation Phase Two

Contents

List of Figures

List of Tables

1 Introduction

In order for individuals to execute accurate and successful movements in the face of ever-changing environmental conditions, constant recalibration of the motor system is required. Motor adaptation, is a form of motor learning that describes the process by which movement errors are used to correct motor output, when previously accurate movements become unsuccessful (Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007). Fatigue, muscle weakening or an altered environment etc. can all be factors in causing motor inaccuracies and stress the importance of adaptation in every-day life.

Motor adaptation can be studied using laboratory-based behavioural experiments which involve the transformation or rotation of visual feedback during pointing/reaching tasks (visuomotor adaptation). Visuomotor adaptation is thought to be largely mediated by error signals derived from discrepancies between the predicted and actual outcome of a movement - a 'sensory prediction error' (Huang, Haith, Mazzoni, & Krakauer, 2011; Wolpert, Diedrichsen, & Flanagan, 2011). Errors in sensory prediction are used to gradually update forward models, which are translated into new motor commands and allow future movements to become increasingly accurate (Shadmehr, Smith, & Krakauer, 2010; Krakauer & Mazzoni, 2011). It is widely accepted that the cerebellum plays a critical role in successful error reduction during adaptation (Tseng et al., 2007; Izawa, Criscimagna-Hemminger, & Shadmehr, 2012). Clinical research supports this notion, as cerebellar patients show impairments or a complete inability to adapt to rotational or forcefield transformations (Maschke, Gomez, Ebner, & Konczak, 2004; Rabe et al., 2009; Werner, Bock, Gizewski, Schoch, & Timmann, 2010). The primary motor cortex (M1) is also considered to be involved in internal model formation and

retention during motor adaptation. Research suggests that M1 may contribute to successful error reduction in visuomotor and forcefield transforms (Li, Padoa-Schioppa, & Bizzi, 2001; Hunter, Sacco, Nitsche, & Turner, 2009). Additionally, disrupting M1 with transcranial magnetic stimulation (TMS) impairs motor memory of the learned adaptive behaviour (Hadipour-Niktarash, Lee, Desmond, & Shadmehr, 2007).

Transcranial direct current stimulation (TDCS) is a form of non-invasive brain stimulation, which applies an electrical current from electrodes on the scalp to targeted brain areas below (Nitsche & Paulus, 2000). Direct current stimulation first gained traction in animal research during the mid 60's, as many studies found that weak currents applied to the scalp or transcranially were capable of modulating resting membrane potentials and thus enhancing or reducing cortical excitability (Creutzfeldt, Fromm, & Kapp, 1962; Eccles, Kostyuk, & Schmidt, 1962; Purpura & McMurtry, 1965). Since these pioneering animal studies, TDCS has gained significant popularity in both human research and clinical settings, due to its capability of modulating neural excitability and enhancing neural plasticity, whilst being safe, painless, non-invasive and simple to apply. TDCS has been shown to work in a polarity dependent manner, with anodal stimulation increasing neural excitability and cathodal stimulation causing a diminution in excitability. Nitsche and Paulus (2000) used TMS over the motor cortex to assess changes in excitability levels after the application of TDCS. They compared motor evoked potentials (MEPs) produced from the TMS before and after either anodal and cathodal stimulation. The authors reported that anodal stimulation significantly increased MEP size and thus cortical excitability, whereas cathodal stimulation reduced MEP size as a result of a decrease in excitability.

Increased neuronal firing rates/depolarisation and shifts in resting membrane potential under the electrodes are thought to underpin augmented cortical excitability during anodal TDCS (Bindman, Lippold, & Redfearn, 1964; Stagg & Nitsche, 2011). Nitsche, Fricke, et al. (2003) highlighted the importance of resting membrane alterations, more specifically sodium and calcium channel conductance, in TDCS induced excitability changes. The authors blocked voltage-gated sodium and calcium channels using carbamazepine and flunarizine respectively and found that the associated increases in cortical excitability during TDCS were eliminated completely or significantly diminished. Sustained excitability after anodal TDCS are suggested to be more likely a result synaptic plasticity and long-term potentiation/depression (LTP/LTD) of synapses (Bindman et al., 1964; Paulus, 2004). A decrease in inhibitory neurotransmitter gamma-aminobutyric acid (GABA) levels under the active electrode is thought to be the cause of prolonged cortical excitability, which also correlates with improvements in motor learning (Stagg, Bachtiar, & Johansen-Berg, 2011; Kim, Stephenson, Morris, & Jackson, 2014). Further neurochemical evidence suggests N-methyl-D-aspartate (NMDA) receptors play a key role in anodal TDCS aftereffects, as long-term MEP facilitation is suppressed by NMDA-receptor antagonists (Nitsche, Fricke, et al., 2003). Protein synthesis and fluctuations in calcium and cAMP, which play key roles in LTP and LTD are also suggested to be involved in sustained cortical excitability after anodal TDCS (Gartside, 1968; Hattori, Moriwaki, & Hori, 1990; Islam, Aftabuddin, Moriwaki, Hattori, & Hori, 1995; Nitsche et al., 2008). The neural mechanisms behind decreases in excitability, both during and after cathodal stimulation, appear to be less clear. It is believed however, that membrane alterations are responsible for diminished cortical excitability during stimulation, whereas modulation of glutamatergic synapes are responsible for longer term effects (Stagg & Nitsche,

2011).

As the cerebellum plays a vital role in motor control and function, an increasing number of studies have investigated the effect of cerebellar TDCS. However, the exact neural mechanisms behind changes in cerebellar excitability post TDCS have been far less researched than those of the cortex and thus still remain somewhat unclear. Changes in purkinje cell activity (the main output of the cerebellar cortex) is theorised to be the most likely cause of alterations in cerebellar excitability (Galea, Jayaram, Ajagbe, & Celnik, 2009; Grimaldi et al., 2016). Cerebellar activity after TDCS can be studied indirectly by means of cerebello-brain inhibition (CBI). CBI refers to the overall inhibitory tone exerted by purkinje cells over M1, via the cerebello-thalamo-cortical pathway (Ugawa et al., 1991; Fernandez, Major, Teo, Byrne, & Enticott, 2017). Anodal cerebellar TDCS is said to facilitate CBI as a result of increased purkinje cell excitability, which increases dentate nucleus inhibition and therefore the excitatory connection to M1 via the ventral thalamus. On the other hand, cathodal stimulation reduces CBI due to decreased purkinje cell excitability and thus reduced inhibition of the excitatory pathway between the dentate nucleus and M1 (Galea et al., 2009). Unlike cortical TDCS no consistent metabolic changes have been found during cerebellar TDCS. Jalali et al. (2018) found no significant changes in GABA or glutamate during or after cerebellar anodal TDCS using magnetic resonance spectroscopy (MRS). Although interestingly, a significant decrease in cerebellar glutamate levels were found, which strongly correlated with motor memory retention.

The effects of TDCS can be measured either online (during the stimulation session) and/or offline (a period after the stimulation has ended). Multiple studies have reported positive online effects of TDCS ranging from improvements in cognitive training (D. Martin, Liu, Alonzo, Green, & Loo, 2014) and working

memory (Fregni et al., 2005) to locomotion adaptation (Jayaram et al., 2012) and serial reaction time (Nitsche, Schauenburg, et al., 2003). Many studies have also displayed lasting effects of stimulation in a variety of different outcome measures. Zimerman et al. (2013) found improvements in complex motor skill learning 24 hours after anodal TDCS; Ehsani, Bakhtiary, Jaberzadeh, Talimkhani and Hajihasani (2016) showed long-term motor learning improvements in a serial reaction time task post TDCS and Reis et al. (2009) reported enhanced offline motor skill acquisition after TDCS sessions. Research has shown that elevations in cortical excitability due to TDCS can be sustained for prolonged periods after stimulation termination (Bindman et al., 1964; Nitsche & Paulus, 2001), which likely explain the longer-term effects. The neural mechanisms behind these improvements in both online and offline contexts are believed to be as discussed in the previous paragraphs.

Due to its capability of enhancing both motor/cognitive function for extended periods of time, whilst also being safe and well-tolerated, TDCS has become an exciting tool in neuro-clinical research. Some research has sought to investigate the effects of cortical stimulation on the symptoms of Parkinson's Disease (PD). Fregni et al. (2006) showed significantly improved motor function and increased MEP size in PD patients after anodal TDCS relative to sham or cathodal stimulation. Other studies have shown enhancements in working memory after anodal TDCS (Boggio et al., 2006) and improvements levodopa-induced dyskinesias after both M1 and Cerebellar stimulation (Ferrucci et al., 2016), further highlighting the potential use of TDCS as an adjunct therapy for PD. TDCS has also often been used in stroke rehabilitation. Stroke survivors frequently experience severe upper limb deficits and paresis, with impairments being more profound distally rather than proximally e.g. hand function (Patten, Lexell, & Brown, 2004). Allman et al. (2016) coupled motor training with ipsilesional anodal TDCS and found improvements in numerous and

generalised upper limb function tests/exercises, as well as increased brain activity during movement for up to 3 months post-intervention. Improvements in motor learning/function, neuro-plasticity and cortical excitability of the affected limb/hemisphere have also been reported post anodal TDCS with some longer term effects (Hummel et al., 2005; Boggio et al., 2007; Lefebvre et al., 2013). Some early work on spinal cord injury (SCI) patients show that TDCS can raise corticospinal excitability to the most affected muscles, induce spinal plasticity and improve specific movement deficits (Murray et al., 2015; Yamaguchi et al., 2016). TDCS has also shown promise in ageing research, as both M1 and cerebellar stimulation can enhance visuomotor adaptation in elderly people (Hardwick & Celnik, 2014; Panouillères, Joundi, Brittain, & Jenkinson, 2015). This research suggests that TDCS can additionally be used to tackle the natural decline in motor function and adaptation associated with increasing age.

As motor adaptation is a robust way to investigate motor learning, performance and function, many recent studies have combined visuomotor tasks with TDCS interventions to further examine the effect of both M1 and cerebellar stimulation on motor adaptation (Block & Celnik, 2013; Reis et al., 2013; Jalali, Miall, & Galea, 2017). Galea et al. (2011) utilised anodal TDCS of both the lateral cerebellum and M1 during a visuomotor rotation reaching exercise, in order to understand more about their respective roles during adaptation. Like others, the authors found that cerebellar stimulation improved adaptation via increased error reduction, whereas M1 stimulation caused a persistence of error during 'no-feedback de-adaptation', which was interpreted as increased retention. These results appear to suggest a clear dissociation between M1 and the cerebellum during visuomotor adaptation; the former involved in retention and the latter dedicated to the adaptive process itself. More recently however, Panouillères et al. (2015), using a similar visuomotor

paradigm, reported results at odds with Galea et al. (2011). They found that M1 stimulation enhanced adaptation for both young and elderly participants, with no effect of cerebellar stimulation. One theory the authors proposed to explain this result is that different movements and effectors were used to complete the tasks; hand/fingers (Panouillères et al., 2015) vs reaching (Galea et al., 2011; Hardwick & Celnik, 2014). It was therefore suggested that given the high level of control exerted by M1 over fine hand and finger movements, it may play a more crucial role in the process of adaptation using the hand, compared to movements of the whole arm.

It has long been suggested that the neural control over reaching and hand/finger movements may be subserved by partially different functional pathways. Primate research revealed the presence of direct cortico-motoneuronal (CM) projections from M1 to motor neurones in the ventral horn of spinal segments (Lemon, 1993; Porter & Lemon, 1993). These monosynaptic connections are thought to be vital for the production of dexterous and fractionated finger/hand movements (Bortoff & Strick, 1993). CM projections have been found to be more powerful and command larger action in distal muscles compared to proximal muscles of the upper limb (Phillips & Porter, 1964; Kuypers, 1981). Lawrence and Kuypers (1968a) also highlighted the importance of the motor cortex for distal muscle control. They bilaterally sectioned the pyramidal tracts of monkeys, at the level of the pyramidal decussation, thereby interrupting cortical efference to the spine from all motor cortical areas, without disrupting input from other subcortical structures i.e. the cerebellum. It was found that the monkeys quickly recovered the ability to reach accurately towards food but were left with sustained and profound deficits in fractionated hand and finger use. On the other hand, lesions to medially descending pathways showed intact hand function but impairments in shoulder and other

proximal limb movements (Lawrence & Kuypers, 1968b). Different structures have been identified as potential contributing sources to reach control, however, mounting evidence points to the cerebellum as a fundamental neural substrate involved in controlling movements using the whole arm. Cerebellar degeneration (Zackowski, Thach, & Bastian, 2002; Smith & Shadmehr, 2005) and selective cerebellar inactivation (Bastian & Thach, 1995; Milak, Shimansky, Bracha, & Bloedel, 1997; J. Martin, Cooper, Hacking, & Ghez, 2000) has shown to cause impaired and inaccurate reaching behaviour. Moreover, the cerebellum's large input to the red nucleus (RN) and vestibular nucleus, each highlighted to be important for reaching movements, further supports its role for proximal upper limb function. This apparent distinction in the control of hand/finger and arm movements begs the question whether stimulation of neural substrates, closely linked to the control of these movements, can enhance adaptation. To our knowledge, no other studies have sought to investigate the roles of M1 and the cerebellum during motor adaptation with respect to control of different movement types.

1.1 Aims and Hypothesis

The intention of the present study was to further elucidate the roles of M1 and the cerebellum during visuomotor adaptation using either hand/finger or whole arm reaching movements. M1, cerebellar or sham stimulation was administered during either a Hand task using a joystick or an Arm task using a robotic manipulandum (vBOT). Both online and short-term offline effects of the stimulation were assessed. It was hypothesised that there would be a double dissociation between stimulation site and effector used, thus M1 but not cerebellar stimulation would improve both online and offline adaptation in the Hand task and vice versa in the Arm task.

2 Methods

2.1 Subject Cohort

Ninety right-handed (self-reported) healthy participants took part in the present study (Male = 44, Female = 46, mean age 19.5 $\pm$ 1.4 years, age range 18-29 years). All subjects were screened for any personal or family history of neurological or other conditions which may impact on their ability or safety to complete the experiment e.g. epilepsy, migraine etc. Participants were all undergraduate students at the University of Birmingham and received 'research credits' that counted towards their degree marks for participating. Prior to their visit to the lab, all participants were naïve to the tasks.

Participants were randomly assigned into either a Hand (joystick) or Arm (vBOT) group and then again to one of three stimulation groups (M1, Cerebellar or Sham).

- Joystick Group: n=45

  M1: n= 15 (8 Males, 7 Females)

  Cerebellar: n= 15 (7 Males, 8 Females)

  Sham: n= 15 (6 Males, 9 Females)

- vBOT Group: n=45

  M1: n= 15 (7 Males, 8 Females)

  Cerebellar: n= 15 (8 Males, 7 Females)

  Sham: n= 15 (8 Males, 7 Females)

All participants gave written consent before taking part and the study was approved by the Science, Technology, Engineering and Mathematics Ethical Review Committee at The University of Birmingham.

2.2 Experimental Design

2.2.1 Hand (Joystick) Task

Participants were seated at a comfortable distance away from a vertical computer screen (22.5cm x 30.5cm), so that they could reach and manipulate a small, sprung joystick (APEM 9000 Series, 75 Hz sampling rate) with their right hand (see figure 1A) . The joystick was 6.5cm in height, 2cm in width and fixed to the desk next to the computer screen with a clamp. The screen displayed a white outlined circle (diameter: 12cm) and a red cursor (diameter: 0.5cm), which was controlled by joystick movement (see figure 2B). At rest the cursor would be located in the centre of the of the circle. During the task a green target (diameter: 0.5cm) would 'jump' from the centre position to one of eight equidistant target locations positioned at 0° and every 45° subsequently around the circle perimeter (at any one time the target would be located either in the centre or one of the target positions). The target would stay in the centre of the circle for 1 second before jumping to the target location, where it would remain for a further second before returning to the centre again. There was no sequence order during the task, the target would appear at each target location the same amount of times in a randomised order. Participants were instructed to make straight, ballistic movements with the joystick towards and through the target and then return to the centre position, without making corrective adjustments. The point where participants' movement crossed the perimeter circle (i.e their final position), would be displayed by an open red circle. Vision of the hand was blocked during the task and participants were asked to refrain from moving their arm/shoulder.

2.2.2 Arm (vBOT) Task

Participants sat comfortably in an armless chair and used their right hand to grasp the handle of a custom-built two-dimensional planar robotic manipulandum which allows movement in the horizontal plane (see figure 1B). The vBOT measured and stored the position, distance and velocity of movement at 1000Hz. The task display was reflected onto a 'semi silver' screen (60cm x 76cm) in front of the participants from a computer monitor (Mac Cinema HD Display) located directly above. Similar to the Hand (joystick) task, the screen displayed a 12cm diameter white outlined circle and a 0.5cm diameter red cursor, which moved in accordance to movement of the vBOT handle (see figure 3). As the task begun, a 0.5cm diameter green target would 'jump' from the centre of the circle to one of the eight target locations situated equidistantly around the circle perimeter (at 0° and every 45° subsequently) at random. At any one time the target would be located either in the centre or one of the target positions. In order to ensure between task validity, the timings were exactly the same at the Hand task; the target would remain in the centre for 1 second and then jump to a target position for a further second, before returning back to the centre. Participants were asked to make single, rapid and uncorrected reaching movements with the vBOT handle towards and through the target, then back to the centre. The room was darkened prior to the start of the task to block vision of the hand/arm underneath the screen as well as 'curtain', which was attached to the vBOT frame and prevented participants viewing their upper arm. To ensure a consistent visual position of the targets and cursor, participants rested their head on a centered on the vBOT framework.

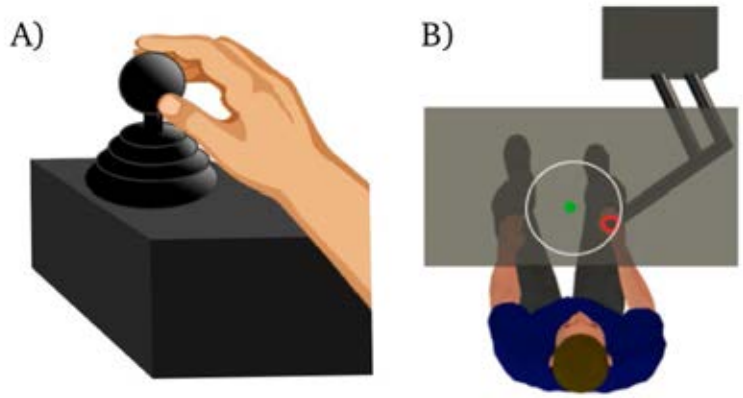

Figure 1: *A schematic diagram of A) the joystick and B) vBOT experimental set up.*

2.2.3 Visuomotor Rotation Paradigm

The task involved baseline, rotational and washout trials. Participants first performed baseline trials, followed immediately by a visuomotor adaptation phase (VMA1) and a 50-minute break period. After the break, participants performed a second visuomotor adaptation phase (VMA2), followed by washout trials (see figure 2). During baseline trials no rotation was applied to the cursor and thus the on-screen cursor would move in the same direction as joystick/vBOT movement. When the two rotational phases began a 60° counter-clockwise (CCW) rotation was applied to the cursor with respect to the joystick/vBOT handle (see figure 3). There was no visual cue to suggest that the rotation had been applied, apart from the cursor displacement to the participants' aimed position. Rotational displacement was returned to 0° during washout trials.

Participants were told that a rotation would be applied at some-point and its nature, but were asked not to use any explicit strategies in order to overcome it. They were simply instructed to try their best to hit or get as close to the target as they could in each trial.

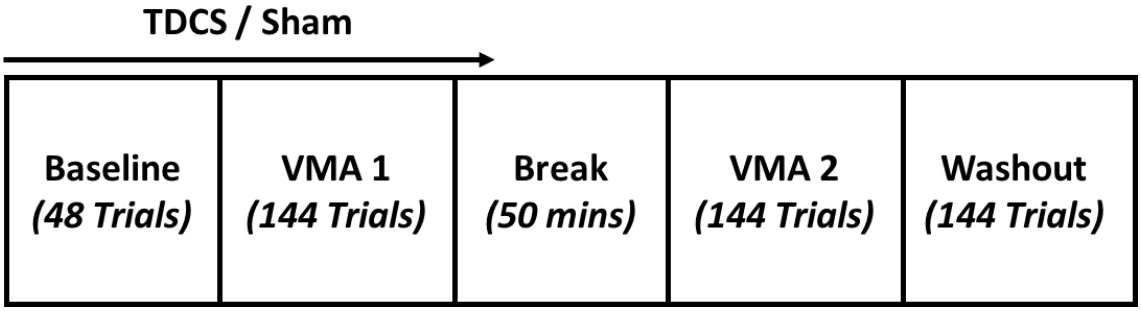

Figure 2: *A time-course of the experimental design outlining trial number during Baseline, VMA1, VMA2 and Washout phases, break duration and TDCS implementation/duration (17 minutes).*

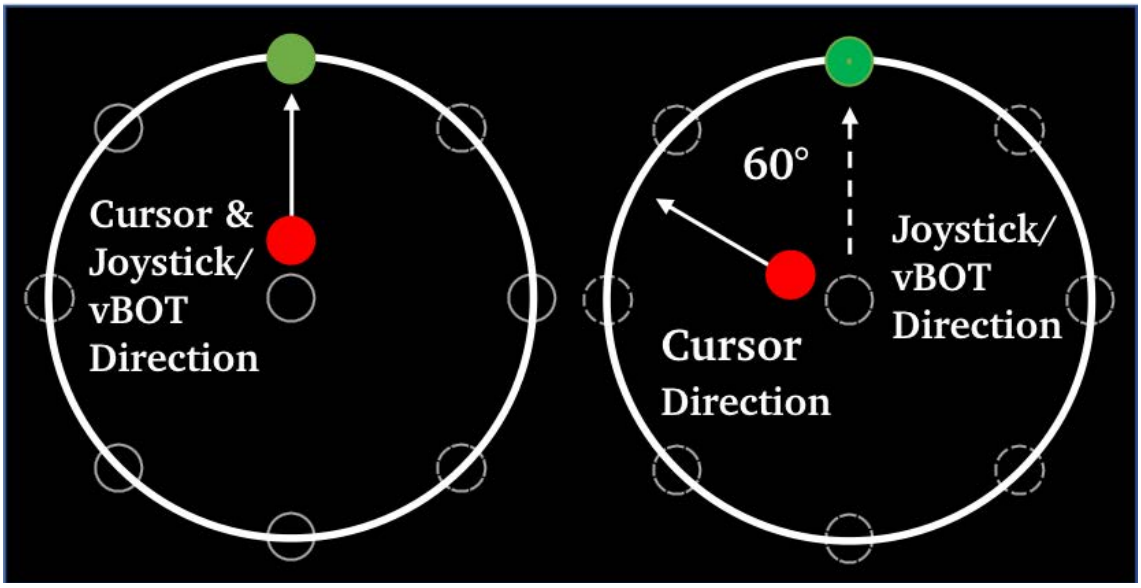

Figure 3: *The display used in both the Joystick and vBOT tasks. Initially, when no rotation is applied both the cursor and participants' aimed movement are the same. However, when a 60° CCW rotation is applied to the cursor participants' aim and cursor direction are mis-matched.*

2.3 TDCS

TDCS was administered via two saline soaked sponge electrodes ($5cm \times 7cm$) using a neuroConn DC-Stimulator. The M1 group had the anodal electrode positioned over the 'hand area' of the left primary motor cortex which was identified for each participant via single pulses of transcranial magnetic stimulation (Boroojerdi et al., 1999) using a MAGSTIM 200 mono pulse stimulator. The cathode electrode was placed over the participants' contralateral supraorbital area (Wagner et al., 2007). For the cerebellar group, the anodal electrode was centered on on the right cerebellar cortex; 3cm lateral of the inion (Galea et al., 2009) and the cathode was placed on the superior aspect of the participants' ipsilateral trapezius muscle. This extra-cephalic montage was selected as it has been found to maximally stimulate cerebellar hemispheres and limit the spread of current to unwanted brain areas (Ferrucci et al., 2013; Ferrucci & Priori, 2014). Similar electrode placements have been used to successfully stimulate the cerebellum and influence behaviour in many published studies (Ferrucci et al., 2013; Ehsani et al., 2016). A series of elasticated and adhesive straps, which passed around and over participants' heads, were used to secure the electrodes in place and ensure they did not slip from their desired position. Stimulation intensity was set at 2mA in both M1 and cerebellar groups. TDCS was gradually ramped on over a 10 second period at the beginning of the baseline phase, it continued throughout the first visuomotor adaptation phase and was then ramped off again, over 10 seconds, 10 minutes into the break period (see figure 2). This totalled a stimulation time of 17 minutes in both active stimulation groups and left 40 minutes of no stimulation during the break (7 Minutes - Baseline & VMA1, 10 minutes - Break). 17 minutes was selected as it has shown to be sufficient in increasing cortical excitability for up to 90 minutes after stimulation

termination (Nitsche & Paulus, 2001) and has resulted in sustained performance improvement after extended break periods (Panouillères et al., 2015).

For Sham stimulation the electrodes were positioned in either M1 or cerebellar montages, chosen at random. In the sham-condition stimulation lasted for 30 seconds and was increased and decreases in a ramp-like fashion over a period of 30 seconds. This method of ramping been found to achieve a high level of blinding, especially when high current intensities are used (Gandiga, Hummel, & Cohen, 2006; Russo, Wallace, Fitzgerald, & Cooper, 2013; van Dun, Bodranghien, Mariën, & Manto, 2016). Measures of perceived comfort and stimulation blinding were assessed via visual analogue scales (VAS) during the break between tasks after the stimulation had ended.

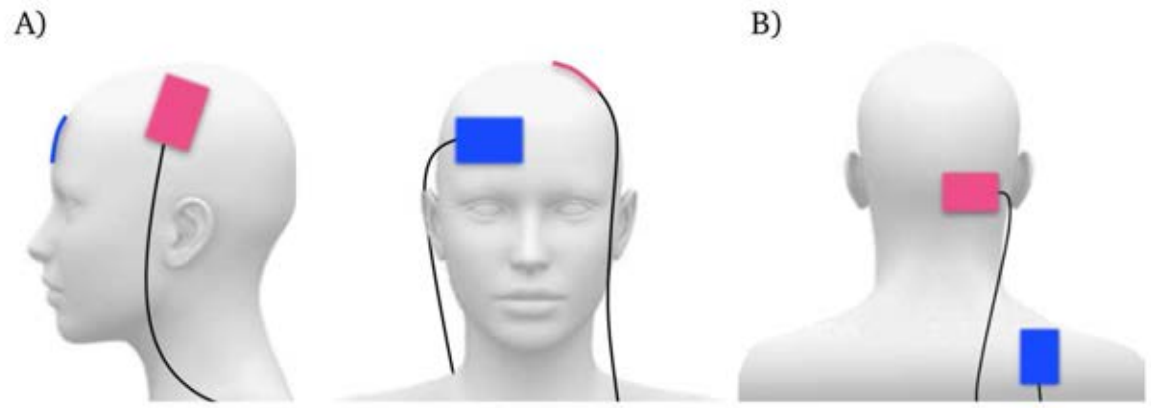

Figure 4: *Example TDCS montages, where A) is M1 stimulation (anode - left hand area of motor cortex, cathode - ipsilateral supraorbital area) and B is cerebellar stimulation (anode - right cerebellar cortex, cathode - ipsilateral trapezius).*

2.4 Data Analysis

The position of the joystick and vBOT handle were tracked trial-by-trial and recorded using custom analysis in MATLAB (version R2017b, Mathworks). The primary outcome measure was the rotational error; defined as the angular displacement between the initial direction of participants' movement at peak velocity and the target location. Peak velocity selections were checked for every trial and adjusted if necessary when a selection was incorrect or missing. Trials were rejected and thus removed from subsequent analysis, if a participant failed to make a movement towards the target, peak velocity was ill defined, and/or more than one movement was made etc. A total of 0.57$\pm$ 1.15 (mean $\pm$standard deviation) trials were rejected per person. Data from each group during baseline, VMA1, VMA2 and washout phases were averaged across bins of 4 trials to be used in further analysis. Late adapted levels during VMA1, VMA2 and washout were taken as an average of the last 30 trials for each participant in each phase, where adaptation/learning plateaued. Early adapted levels were determined by averaging the initial 20 trials for each participant during VMA1 and VMA2.

All statistical analyses were carried out in SPSS Statistics (IBM, version 24). Baseline differences were analysed using 1-way ANOVAs with bins (1-12) as the within-subject factor and stimulation group (M1, Cerebellar and Sham) as the between subject factor. Adaptation/de-adaptation was quantified using separate repeated measures ANOVAs for VMA1, VMA2 and washout, with bins (1-36) as the within group factor and stimulation group as the between subject factor. 1-way or RM ANOVAs were used to analyse differences during early or late adaptation between the different stimulation groups and experimental phases. Tukey corrections were used for 1-way ANOVAs and Bonferroni corrections for RM ANOVAs

to account for multiple comparisons in post-hocs. Greenhouse-Geisser degrees of freedom corrections were used if Mauchly's test of sphericity assumptions of variance were violated. Statistical significance was set at $p < 0.05$.

3 Results

3.1 No differences in baseline performance

A 1-way ANOVA revealed no significant main effect for Stimulation Group during baseline performance in the Arm (vBOT) task; $F_{(2,42)} = 0.59,\ p = 0.56$ (see figure 5). Post hoc tests showed no significant differences between the M1, Cerebellar or Sham group during the baseline phase (p>0.05). Similarly, there was no main effect of Stimulation Group during the baseline phase in the Hand (joystick) task ($F_{(2,42)} = 0.93,\ p = 0.40$) and all post hocs between groups were non-significant (p>0.05, see figure 5). These analyses suggest that stimulation type had no effect on accuracy to the target during baseline in either task.

3.2 Cerebellar stimulation enhanced adaptation during VMA1 in the Arm task

Differences in adaptation between stimulation groups during the Arm task were analysed using a RM ANOVA across all 36 bins of VMA1. Analysis revealed a significant main effect for Bins; $F_{(14,573)} = 152.23,\ p < 0.01$, suggesting that participants in the three stimulation groups were able to successfully reduce their error trial-by-trial throughout VMA1 (see figure 5). There was a non-significant Bin*Stimulation Group interaction ($F_{(27,573)} = 1.07,\ p = 0.37$), likely due to the similarity in adaptation rate between groups, however a significant between subject

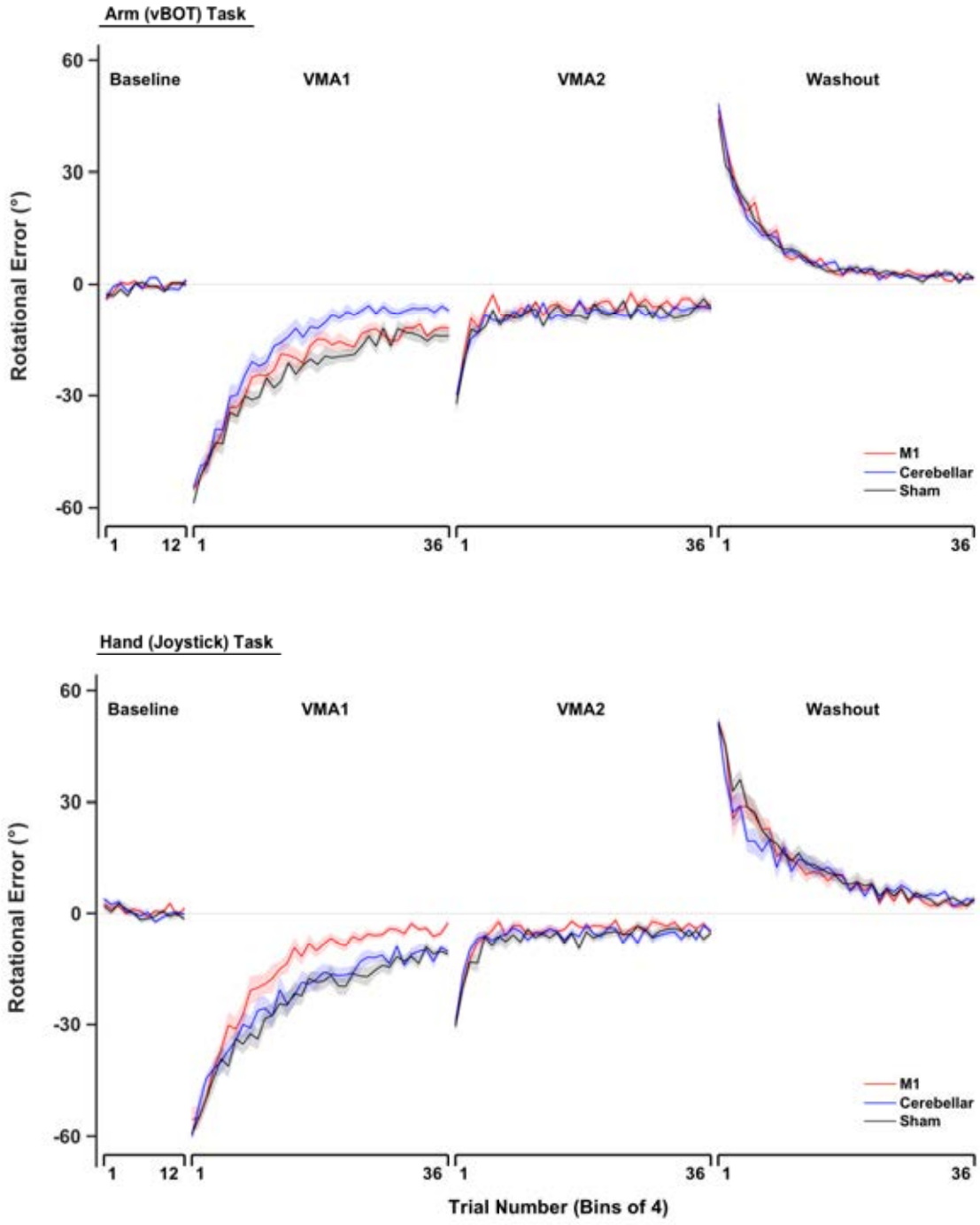

Figure 5: *Mean rotational error (±SEM: shaded areas), averaged every four trials into Bins, for the Arm task (top) and Hand task (bottom) in all stimulation groups during; Baseline (no rotation), VMA1 (60° CCW rotation), VMA2 (60° CCW rotation) and Washout trials (no rotation).*

factor for Stimulation Group was found ($F_{(2,42)} = 9.11,\ p < 0.01$). To further elucidate this group difference during VMA1, the last 30 trials for each participant were averaged and compared using a 1-way ANOVA (between subject factor: Stimulation Group, within subject factor: Rotational Error). Post hoc analysis suggests that cerebellar stimulation improved adaptation during the Arm task as the Cerebellar group were able to reduce their error significantly more than both the M1 and Sham group during late adaptation; $p < 0.05,\ p < 0.01$, respectively (see figure 6A). There was no significant difference in late adapted levels between the M1 and Sham stimulation group, $p = 0.42$.

3.3 M1 stimulation improved adaptation during VMA1 in the Hand task

A separate RM ANOVA was run to test for differences in adaptation between stimulation groups for the Hand task during VMA1. All participants showed the ability to adapt to the rotation and significantly reduce error during the phase (main effect of Bins: $F_{(9,385)} = 173.12,\ p < 0.01$), see figure 5. There was a trend to a significant Bins*Stimulation Group interaction; $F_{(18,385)} = 1.61,\ p = 0.053$, which is probably a result of greater disparity between the M1 group and Cerebellar/Sham groups during VMA1. Like the Arm task, there was a significant between subject effect of Stimulation Group ($F_{(2,42)} = 7.33,\ p < 0.01$). A further 1-way ANOVA comparing late adapted levels between participants in the different stimulation groups revealed that rotational error for the M1 group was significantly lower than that of both the Cerebellar and Sham groups; $p < 0.01$ (see figure 6B). There was no significant difference in late adapted levels between the Cerebellar and Sham group ($p = 0.99$). These results suggest a facilitative effect of M1 stimulation during the hand task.

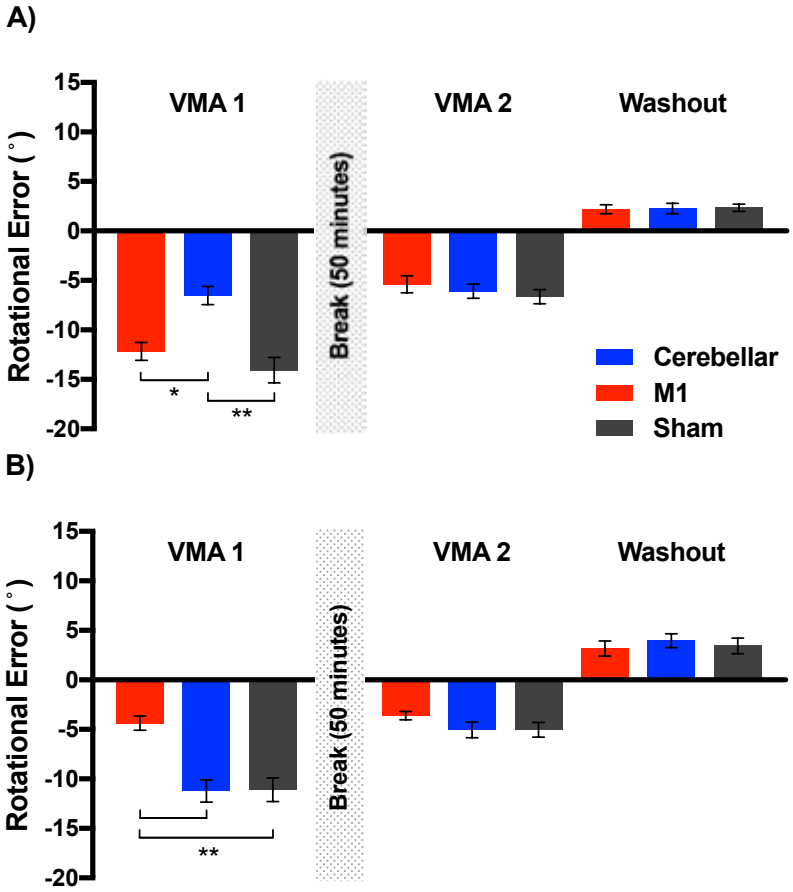

Figure 6: *Average rotational error (±SEM) of the last 30 trails during VMA1, VMA2 and Washout for all stimulation groups in the Arm task (A) and Hand task (B). Statistically significant differences between groups are indicated via * = $p < 0.05$ and ** = $p < 0.01$ following 1-way ANOVAs.*

3.4 No offline effect of stimulation on VMA2 or Washout performance in either task

Separate RM ANOVAs were performed on mean error averaged across the 36 bins in VMA2 and Washout for both tasks. In the Arm task, participants were again able to reduce their error from the beginning to the end of the phase in all groups (main effect Bins: $F_{(16,680)} = 38.06,\ p < 0.01$), see figure 5. There was no effect of Stimulation Group on performance during VMA2 ($F_{(2,42)} = 2.23,\ p = 0.12$) and no

Bins*Stimulation Group interaction ($F_{(32,680)} = 1.34,\ p = 0.10$). Post hocs from a 1-way ANOVA found no significant difference in late adapted levels between groups $p = 0.80$ (M1 vs Cerebellar), $p = 0.50$ (M1 vs Sham) and $p = 0.87$ (Cerebellar vs Sham), see figure 6A. After the rotation is removed, all participants performing the Arm task were able to de-adpat and gradually return to near baseline levels of accuracy, shown by a significant main effect of Bins; $F_{(10,405)} = 204.37,\ p < 0.01$ (see figure 5). There were no Stimulation Group differences during the washout phase ($F_{(2,42)} = 0.53,\ p = 0.95$) and no Bins*Stimulation Group interaction ($F_{(19,405)} = 1.14,\ p = 0.30$). At the end of the washout phase there were no late de-adaptation differences between groups $p = 0.99$ (M1 vs Cerebellar), $p = 0.97$ (M1 vs Sham) and $p = 0.99$ (Cerebellar vs Sham), see figure 6A.

RM ANOVAs for VMA2 and Washout during the Hand task show comparable results. There was a significant main effect for Bins; $F_{(14,588)} = 49.62,\ p < 0.01$, suggesting that participants were able to adapt to the rotation and reduce error a second time throughout VMA2 (see figure 5). There was no differences between groups, shown by a non-significant between subject effect for Stimulation Group ($F_{(2,42)} = 2.06,\ p = 0.14$) and no Bins*Stimulation Group interaction ($F_{(28,588)} = 70.37,\ p = 0.12$). Participants in all groups reached a similar level of accuracy at the end of VMA2 (see figure 6B), which was shown by non-significant post hoc results following a 1-way ANOVA; $p = 0.29$ (M1 vs Cerebellar), $p = 0.30$ (M1 vs Sham) and $p = 1.0$ (Cerebellar vs Sham). All participants performing the Hand task were able to return their error levels to close to zero after the rotational displacement was removed (main effect for Bins: ($F_{(7,299)} = 140.40,\ p < 0.01$), see figure 5. As all Stimulation groups performed almost identically during this phase there was no significant Stimulation Group effect ($F_{(2,42)} = 0.26, p = 0.77$) and no Bins*Stimulation Group interaction ($F_{(14,299)} = 1.50,\ p = 0.11$). 1-way ANOVA post

hocs from the last 30 trails of Washout showed no significant difference between Stimulation Groups; $p = 0.74$ (M1 vs Cerebellar), $p = 0.97$ (M1 vs Sham) and $p = 0.87$ (Cerebellar vs Sham), see figure 6B.

These results suggest that TDCS stimulation had no lasting effect on performance during re-adaptation during VMA2 or de-adaptation during Washout in either task.

3.5 Learning from VMA1 aided initial performance in VMA2

Savings were assessed by comparing the early adapted levels for each participant during VMA1 and VMA2. RM ANOVAs were run using the initial 20 trials for every participant in each stimulation group, with Phase (VMA1/VMA2) as the within group factor and Stimulation Group as the between subject factor. All participants performing the Arm task showed savings from adaptation to the 60° rotation during VMA1 (see figure 7A), as their rotational error was significantly lower at the beginning of VMA2 (main effect of Phase: $F_{(1,42)} = 679.08,\ p < 0.01$). Post hoc analysis showed that all Stimulation Groups (M1, Cerebellar and Sham) had significantly less error at the beginning of VMA2 compared to that of VMA1, $p < 0.01$. All groups performed similarly during early adaptation shown by a non-significant main effect for Stimulation group ($F_{(2,42)} = 0.49,\ p = 0.61$).

It was a similar story for the Hand task. All Stimulation Groups displayed a reduced level of error early in VMA2 compared to early in VMA1, shown by a significant main effect for Phase $F_{(1,42)} = 767.66,\ p < 0.01$ (see figure 7B). Post hocs revealed all Stimulation Groups had significantly lower error during the first 20 trials of VMA2 compared to VMA2, $p < 0.01$. There were no significant differences between Stimulation Groups ($F_{(2,42)} = 0.55,\ p = 0.58$) during early adaptation in VMA1 and VMA2. In order to provide sounder evidence for the presence of savings between the tasks, more sophisticated curve fitting analysis would be desired.

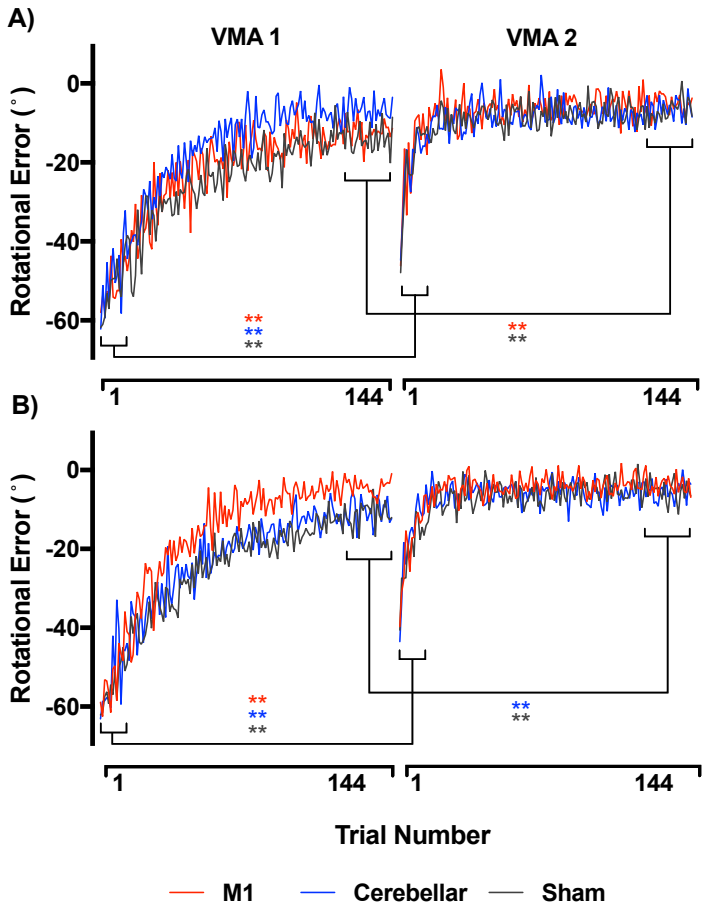

Figure 7: *Mean rotational error for the Arm task (A) and Hand task (B) in all stimulation groups during VMA1 and VMA2. Statistically significant differences between early adapted (first 20 trials) and late adapted (last 30 trials) levels between phases are indicated via * = $p < 0.05$ and ** = $p < 0.01$ following repeated measures ANOVAs (* are colour co-ordinated to the legend).*

3.6 Some, but not all, groups improved late adapted levels from VMA1 to VMA2

RM ANOVAs were used to asses improved late adapted performance between VMA1 to VMA2 and potential offline effects of the stimulation. There was a significant main effect of Phase; $F_{(1,42)} = 66.30,\ p < 0.01$ for the Arm task, suggesting that, on the whole, participants were able to adapt more to the rotation during VMA2. Post

hocs reveal that both the M1 and Sham group reduced error significantly more during VMA2 compared to VMA1 ($p < 0.01$), see figure 7B. The Cerebellar group showed some improvements in error reduction from VMA1 to VMA2, however, this was not significant ($p = 0.68$). The lack of significant improvements made by the Cerebellar group suggests there was little room for further error reduction after VMA1. In contrast, the M1 and Sham groups reduced error significantly less during VMA1 and therefore had greater 'room for improvement' during VMA2.

A similar result was observed for the Hand task, as there was an overall a significant main effect of Phase $F_{(1,42)} = 103.93,\ p < 0.01$, implying improved task performance during the second phase of the experiment. Both the Cerebellar and Sham groups showed significant error reduction from late VMA1 to late VMA2; $p < 0.01$ (see figure 7B). As a result of a more complete adaptation during VMA1, the M1 group did not significantly reduce their late adapted levels from VMA1 to VMA2. Despite performance being closer to baseline during late VMA2, this difference was not significant ($p = 0.30$) and can likely be attributed to achieving near baseline levels of performance during VMA1.

3.7 No difference in perceived comfort or stimulation levels

To ensure effective blinding of stimulation type (Anodal or Sham), all participants rated their perceived comfort and stimulation confidence on a 10-point VAS (see Table 1). 1-way ANOVAs with the between subject factor of Group (Hand task: M1, Cerebellar and Sham; Arm task: M1, Cerebellar and Sham) and within subject factor of Perceived Comfort or Perceived Stimulation were performed. All groups reported a high comfort level (low-mid 3's on the VAS) and there was no significant differences between groups (main effect of Group: $F_{(5,84)} = 0.38,\ p = 0.86$).

Importantly, there was also no significant differences between the six groups for

perceived stimulation; $F_{(5,84)} = 0.293,\ p = 0.92$ with all groups reporting high confidence that they were in an active stimulation group (High 7's/low 8's on the VAS), rather than in a placebo group. All post hocs from 1-way ANOVAs showed no significant differences between the individual groups ($p > 0.05$). These results suggest a high level of blinding was achieved with regards to whether participants received active or sham stimulation.

Perceived Comfort (1-10)					
Arm (vBOT) Task			Hand (Joystick) Task		
M1	Cerebellar	Sham	M1	Cerebellar	Sham
3.27	3.07	3.53	3.13	3.33	3.07
± 1.16	± 1.16	± 1.06	± 1.13	± 1.11	± 1.22
Perceived Stimulation (1-10)					
Arm (vBOT) Task			Hand (Joystick) Task		
M1	Cerebellar	Sham	M1	Cerebellar	Sham
8.27	7.60	7.80	7.87	7.93	7.87
± 1.67	± 1.18	± 1.37	± 1.51	± 1.91	± 1.68

Table 1: *Perceived Comfort and Stimulation scores ($\pm$ SD) rated by participants in each stimulation group for both the Arm and Hand tasks on a 1-10 point VAS (1 being low, 10 being high).*

4 Discussion

The aim of the present study was to investigate the roles of the cerebellum and M1 during visuomotor adaptation using either hand/finger or whole arm movements to complete the task. The intention was to see if stimulation of these brain regions could produce a differential effect on the performance of specific movement types. It was

hypothesised that, due to their respective functional control of different movements, cerebellar stimulation would enhance adaptation in the Arm task and M1 TDCS would do similarly in the Hand task. The findings of the present study are two-fold; TDCS over M1 improved adaptation compared to cerebellar and sham stimulation in the Hand (joystick) task during VMA1, whereas cerebellar TDCS increased adaptation during VMA1 in the Arm (vBOT) task, with no effect of M1 stimulation. Interestingly, there was no apparent offline effect of the stimulation during VMA2 after the 50 minute break as all stimulation and sham groups performed similarly.

When initially exposed to a visuomotor rotation, individuals make large movement errors. However, after continued experience of the transformation they are able to gradually reduce errors and produce increasingly accurate movements. Sensory prediction errors and updating internal models of movement are thought to be the driving force behind an individual's ability to adapt to perturbing forces (Wolpert & Flanagan, 2001; Tseng et al., 2007; Shadmehr et al., 2010). It is suggested that the mismatch between predicted and actual consequences of movements during visuomotor tasks allow forward models in the cerebellum to be updated, leading to gradually increasing accuracy (Blakemore, Frith, & Wolpert, 2001). Despite some differences in the amount of adaptation in the present study, all three stimulation groups in both the Arm and Hand tasks were able to adapt behaviour and reduce error throughout VMA1 to levels close to that of baseline performance. As all groups displayed successful adaptive behaviour, it can be assumed that stimulation is not necessary to drive the adaptive process to rotation. However, the clear dissociation between stimulation site and effector used, suggests a specific effect of TDCS on different movement types during adaptation tasks.

Enhanced performance during VMA1 due to M1 TDCS in the Hand task replicates findings from previous adaptation and motor learning studies which also

involve hand movements (Nitsche, Schauenburg, et al., 2003; Kantak, Mummidisetty, & Stinear, 2012; Panouillères et al., 2015). The proposed theory is that as M1 exerts a high level of control over fine and independent hand/finger movements, it stands to reason that it would play a greater role in the process of controlling hand movements during adaptation. As aforementioned, direct CM projections from M1 to motor neurones that control distal muscles, allow for precise manual dexterity in humans and some primates (Bortoff & Strick, 1993; Lemon, 1993). In addition to the evidence presented by Lawrence and Kuypers (1968a) many other studies have also demonstrated the importance of M1 and CM projections to the production of relatively independent finger, hand and grasping movements by lesioning tracts and recording from neurones. Lawrence and Hopkins (1976) interrupted cortico-spinal fibres via pyramidal tract lesions of newborn rhesus monkeys and found that independent movements of the fingers never developed. Furthermore, the firing pattern of neurones in M1 strongly suggests that it plays a vital role in producing precision grip and synchronous grasping movements (Muir & Lemon, 1983; Lemon et al., 2007). Maps in M1 also have disproportionately large representations of the hands and thus devote many more neurones to hand/finger muscles compared to others which may be much greater in mass and volume (Cheney, Fetz, & Mewes, 1991). Given the crucial role of M1 to the production of hand and finger movements, it is suggested that stimulation during the Hand task increased the excitability of M1 and thus CM projections to distal upper limb muscles. As a result, participants were able to better execute movements towards the target and thus learn and adapt to the rotation more successfully than participants in either the cerebellar or sham groups. Similar improvements in hand use and function after TDCS have also been displayed in stroke patients (Hummel & Cohen, 2006; Allman et al., 2016). This result is in direct conflict with other

visuomotor adaptation studies which report that cerebellar TDCS increases the rate of adaptation with either no effect of M1 stimulation or only an increase in retention (Galea et al., 2011; Block & Celnik, 2013; Hardwick & Celnik, 2014). The authors theorised that, stimulation drives a plastic mechanism in the cerebellum and increases the response to error. It should be noted however, that different movement types were used in order to complete the tasks. All three of the above studies required reaching movements towards the targets, involving some form of co-ordinated proximal upper limb manipulation, whether with a digitised pen or a robotic device. In contrast, during the present study only the hand and fingers were used to move the joystick and participants were asked to refrain from moving their arm. Rather than the plastic effect cited previously and considering the neural control underlying the different movement types, we believe that M1 plays more significant role in the processes that adapt hand movements, compared to those of reaching movements, which are under greater cerebellar control.

Some have also speculated that it is the size of rotation, 60° as opposed to 30° in many other studies (Krakauer, Ghez, & Ghilardi, 2005; Krakauer, Mazzoni, Ghazizadeh, Ravindran, & Shadmehr, 2006; Galea et al., 2011), that may have caused the improved performance after M1 stimulation (Panouillères et al., 2015; van Dun, Bodranghien, Manto, & Marien, 2017). Adaptation to larger rotations is thought to rely on more explicit processes which are suggested to have a more cortical locus, whereas adaptation to smaller rotations is more implicit and thus cerebellar dependent (Heuer & Hegele, 2008). However, evidence suggests that it is not possible to successfully implement an explicit strategy during a visuomotor adaptation task with a rotation as large as 45° implicit (Mazzoni & Krakauer, 2006). The authors report a conflict between implicit learning and an explicit strategy, in which the implicit plan overrides the strategy. Additionally, if this was the case, M1

stimulation should have enhanced adaptation in both tasks not just the Hand task, as the rotation was exactly the same.

In the Arm task, cerebellar but not M1 stimulation improved adaptation and resulted in a better task performance during VMA1. This result is not out of place within the current literature, as many previous studies have reported a beneficial effect of cerebellar stimulation on visuomotor adaptation. The most common hypothesis suggests that purkinje cell response to error signals transmitted by the climbing fibres are modulated by the stimulation. This may result in plastic mechanisms such as LTD and increase purkinje cell, and thus cerebellar, responsiveness to error during adaptation (Galea et al., 2011). If the stimulation had resulted in secondary plastic events in the cerebellum and increased response to error, it would be assumed that adaptation would be enhanced in both tasks. However, cerebellar stimulation only contributed to improved adaptation in the Arm task and not the Hand task. Whilst the evidence supporting the crucial role of the cerebellum during adaptation cannot be refuted (Wolpert, Miall, & Kawato, 1998; Donchin et al., 2011), it must be speculated that cerebellar TDCS might have had a different effect on adaptation during the present study.

The cerebellum has long been suggested to be pivotal for motor control. Cerebellar control of movement is ipsilateral and therefore influences motion on the same side of the body (Brooks, Thach, et al., 1981). In order to achieve this, it is believed that many cerebellar outputs to motor systems are doubly crossed (Gibson, Horn, Pong, & Van Kan, 1998), as opposed to many of motor cortical tracts which cross once at the level of the pyramidal decussation and exert their effect contralaterally or some that do not cross at all (Brinkman & Kuypers, 1973). Research suggests that the cerebellum is a neural substrate especially involved in the

control of accurate and coordinated, multijoint upper limb reaching movements (Bastian, Martin, Keating, & Thach, 1996; Schweighofer, Spoelstra, Arbib, & Kawato, 1998; Topka, Konczak, Schneider, Boose, & Dichgans, 1998). Cerebellar ataxia or degeneration often causes deficits in reach behaviour characterised by; overshoot, a lack of sufficient muscle torque and uncoordinated or asynchronous arm movements (Smith & Shadmehr, 2005; Bhanpuri, Okamura, & Bastian, 2014). Fortier, Kalaska, and Smith (1989) recorded from 312 cerebellar neurones with proximal upper limb receptive fields and found firing behaviour was consistent with a role in controlling reaching movements. Additionally, lesions to or inactivation of the deep cerebellar nuclei (DCN), the sole output of the cerebellum, have shown to cause reaching impairments. Milak et al. (1997) separately inactivated the fastigial, interposed and dentate nuclei of cats. They found that inactivation of each DCN caused attenuated spatial and temporal features of the learned reaching movements, with interposed nuclei inactivation resulting in the most serious kinematic deficits. The results of this study clearly suggest an important role of the cerebellum in the organisation and execution goal-directed upper limb movements. A further study found that patients with dentate nuclei lesions displayed profound reaching deficits (Bastian & Thach, 1995). The RN, which receives large input from the contralateral cerebellum, is also suggested to be significant for the control and execution of proximal limb and reach behaviour via the rubrospinal tract (Keifer & Houk, 1994).

In accordance with the conclusions drawn regarding M1 TDCS during the Hand task, it is suggested that as the cerebellum is critical to the execution of successful and coordinated reaching movements, it is key to the processes that adapt movements of the arm. In other words, it is theorised that TDCS over the cerebellum allowed participants to make more effective reaching movements towards the targets, which resulted in better performance and improved learning compared to the M1 or Sham

groups during VMA1. Increased CBI could be a mechanism to further explain a better task performance in the cerebellar TDCS group during the Arm task. It is known that cerebellar TDCS increases CBI (Galea et al., 2009), which has also been suggested to be correlated with precision behaviours (Caligiore et al., 2017). From this, it could be implied that increased CBI, due to the stimulation, improved state estimation of limb position during the task and resulted in more precise reaching movements and thus enhanced learning/adaptation. Increased excitation of the cerebello-rubral pathway could also be a contributing factor towards the enhanced adaptation in the cerebellar group, considering its suggested influence over proximal limb movements.

Despite the conclusions made regarding the effect of M1 and cerebellar TDCS on the different tasks, it is by no means suggested that the control of hand/finger and reaching movements are entirely functionally distinct. M1 is known to be heavily involved the execution of all voluntary movements (Kakei, Hoffman, & Strick, 1999; Sanes & Donoghue, 2000), including reach/upper limb movements and the cerebellum has also been shown to contribute to some grasping/pinching functions (Gibson et al., 1998; Glickstein, Waller, Baizer, Brown, & Timmann, 2005). Additionally, other neural substrates such as; the premotor, supplementary and posterior parietal cortices all play important roles in the planning and implementation of many different types of both hand and arm movements (Filimon, 2010). However, given the double dissociation between stimulation site and effector used during the task, it appears most likely that enhanced learning occurred during tasks when brain areas, which impose greater control over the movement type involved, were stimulated. This hypothesis is furthered by the strong functional and behavioural evidence pointing to the importance to M1 for distal and the cerebellum in more proximal upper limb use mentioned previously.

Surprisingly, no apparent offline effect of the TDCS was observed after the break period. In both tasks, the M1, cerebellar and sham groups performed similarly during VMA2. Upon re-exposure to the rotation after the 50 minute break (40 minutes with no stimulation), all six groups displayed savings of the previously learned visuomotor transform. Savings is defined as quicker and more complete learning when re-exposed to the visuomotor rotation after a undetermined period of time (Krakauer, 2009). This finding is displayed by a reduced initial error, a much steeper learning curve and smaller errors at the end of VMA1 compared to VMA2. It is suggested during a period of rest, the memory trace of the learned rotated state is consolidated and therefore when re-exposed to the rotation, the rate of adaptation is quicker (Doyon et al., 2009). TDCS had no effect on savings/consolidation, as the M1 and cerebellar groups performed similarly to the sham groups in both tasks. As the M1 group in the Hand task and cerebellar group in the Arm task had more complete and enhanced adaptation during VMA1, it might have been expected that these groups would have displayed increased savings. However, in this case it appears that either the break between tasks decayed the motor memory of all groups to a similar level, or all groups attained a level of adaptation that allowed for successful transfer.

Neither the M1 group in the Hand task nor the cerebellar group in the Arm task displayed a continued benefit of the stimulation compared the respective other groups during VMA2. There are two potential explanations for this result 1) the stimulation length was not sufficient enough to maintain increased excitability of stimulated regions or 2) there was little further room for improvement, as these groups had already attained a near baseline level of accuracy towards the end of VMA1, or in other words a ceiling effect. It is unlikely that the stimulation length (17-minutes) was not long enough to maintain increases in excitability beyond the

break, as Nitsche and Paulus (2000, 2001) showed stimulation between 9-15 minutes produced lasting effects for up to an hour. Additionally, Panouillères et al. (2015) found that adaptation remained improved in certain groups after a 40-minute break with no stimulation (the same stimulation time and break period was used in the present study). Therefore, it is most likely that the lack of further improvements in performance for the M1 and cerebellar groups during VMA2, in their respective tasks, is as a result of a ceiling effect. A ceiling effect occurs when the highest or near highest measurement/score is attained and thereby the chances of improving to a greater extent are decreased. In this case, as both of the groups were close to achieving 0° error towards the end of VMA1 there was no real room to reduce error more during VMA2. Interestingly, the cerebellar group in the Hand task and the M1 group in the Arm task did significantly improve performance from the end of VMA1 to the end of VMA2. This is unlikely to be an offline effect of the stimulation as both the respective sham groups performed similarly. Significantly better performance in VMA2 could be attributed to a performance effect. Continued exposure to the rotated state allowed participants in these groups to become more familiar with the task and as a result get better at it, thus reducing error more effectively.

All groups displayed large aftereffects at the beginning of washout trials, but were able to gradually de-adapt and return to a baseline level of performance by the end. Aftereffects occur due to the storage of an updated forward model and show that adaptation is not a simple reaction but a sophisticated mechanism of prediction and feedback (Werner et al., 2010). The size of aftereffects and de-adaptation rate was similar for all groups in the respective tasks as they all attained a very similar level of adaptation during VMA2.

4.1 Recent TDCS contention and associated limitations

Over the past decade or so the number of TDCS studies has increased significantly and it is now a very popular technique in neuroscience research. However, as the popularity of TDCS has increased, so have the caveats to its use. A growing number of studies have reported inconsistent, highly variable and/or null results (Laakso, Tanaka, Koyama, De Santis, & Hirata, 2015; Jalali et al., 2017). In order to reliably establish the effects and mechanisms of TDCS, there has been increasing calls for better controlled, single/double blinded studies with higher power, especially if TDCS is to be used as a viable clinical tool. Sham groups were used in the present study to act as controls and sufficient stimulation ramping was used to ensure all participants were unaware of their grouping. Unfortunately, due to time and availability constraints, the study could only be single blinded rather than double. However, it is highly unlikely that experimenter blinding would have altered the results. Comparable if not higher participant numbers were used in the present study to establish high external validity and prevent individual differences confounding the results. A previous TDCS study calculated that groups of up 45 participants per group was necessary in order to produce significant differences (Jalali et al., 2018). However, groups of 15 participants was sufficient to reveal significant adaptation differences and it is difficult to speculate whether additional power would have affected these results. The use of different electrode montages can be a limitation of TDCS and has also been attributed to the variable results found in the literature. Small adjustments to electrode placement can have vast effects on the flow of current to the brain (Woods et al., 2016). As motor maps in the brain differ slightly between individuals, TMS was used to locate the 'hand area' accurately in each participant receiving M1 stimulation (Boroojerdi et al., 1999).

This method is much more reliable than purely measuring each participant's head or using the 10-20 system. For cerebellar stimulation, many previous studies have placed the reference electrode over the buccinator muscle (Galea et al., 2011; Herzfeld et al., 2014). However, as mentioned before, recent modelling studies suggest that placing the reference electrode on the shoulder maximises current delivered to the cerebellar hemispheres and reduces current spread (Ferrucci et al., 2013; Ferrucci & Priori, 2014). Modelling studies, such as these, are important for TDCS research as they allow for more precise electrode placement/montages and thus increase the potential for reliable and replicable results. Given the limitations surrounding TDCS research at present, particular attention was dedicated to the stimulation protocol in order to maximise the reliability and validity.

4.2 Conclusion

The results of the present study leads to the conclusion that there may be a functional distinction between the control of hand/finger and whole arm reaching movements during visuomotor adaptation. TDCS over M1 significantly improved adaptation during the Hand task in VMA1 compared to cerebellar or sham stimulation, whilst cerebellar TDCS significantly enhanced adaptation in the Arm task during VMA1 compared to M1 or sham stimulation. It is believed that stimulation of brain areas, which exert a high level of control over different movement types, allowed for a better and more accurate performance in the respective tasks and therefore produced greater learning. This result may highlight an alternative mechanism as to how TDCS works in a motor leaning/performance context during specific tasks. In addition these results could provide key insight into the use of TDCS in rehabilitation for different upper limb deficits. Previous studies have shown some positive results when TDCS is coupled with motor training

(Hummel et al., 2005; Bolognini et al., 2011; Allman et al., 2016), however, many improvements reported are often limited to a portion of the upper limb or only enhance activity rather than functionality. Results presented here would suggest that TDCS over M1 and the cerebellum could produce a more effective strategy for rehabilitation of the entire upper limb. Further and more diverse research investigating the effectiveness of TDCS as an adjunct therapy for rehabilitation of upper limb motor disorders is required in order to support this and for TDCS to have more clinical relevance.

4.3 Future Directions

Future work will look to extend upon the ideas of this thesis and gain a more thorough understanding of the roles of M1 and the cerebellum in upper limb motor control. One of the next logical steps would be to use cathodal TDCS to decrease neural excitability of M1 and the cerebellum and asses the effects on performance in both tasks. Based on results found here, it would be expected that cathodal stimulation will impair performance where anodal TDCS enhanced it. Future studies could also look to develop a number of different tasks, in order to see if the effects observed here can be generalised beyond visuomotor adaptation to skill learning, rehabilitation tasks etc. Additionally, TMS could be used to measure changes in neural excitability after anodal/cathodal or sham stimulation, which could provide solid neurophysiological data to support behavioural results. The basis of this study could also be extended to test elderly and patient populations - who suffer from upper limb deficits - to see if cerebellar and M1 stimulation can be effective for hand/finger or whole arm reaching rehabilitation and promote functional gains. Furthermore, repeated testing sessions of stimulation and training, with longer-term follow up assessments, should be used in future studies. This will help to give a more comprehensive understanding of how

M1 and cerebellar TDCS could be used as a clinical treatment for proximal and distal upper limb deficits.

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6 Appendix

The Role of the Cerebellum and Motor Cortices in Motor Learning Using Movements of the Hand or Arm

You have expressed an interest in participating in a study which aims to examine the roles of the cerebellum and motor cortices during a motor learning task that uses either movements of the hand or whole arm. This study forms a step-in understanding to which parts of the brain control how skills are learnt and remembered with different parts of the body, and should lead to a better understanding of motor learning.

Practical matters

If you agree to participate, we would ask you to come to the School of Sport Exercise and Rehabilitation Sciences (room 222c). The session will take no more than 2 hours. This will be ample time to explain the procedures and to answer any questions you may have. You will receive transcranial direct current stimulation (TDCS) for no more than 20 minutes during the task. We will reimburse you with research credits for your time (or £10 per hour if arranged prior to the session).

The Task

You will perform a task where you will be asked to control a cursor on a screen and move it towards visual targets from a central starting position using either your whole right arm, or just your right hand. The main aim is to hit the target as accurately as possible throughout the study. You will perform the task in two blocks with a break in between. During the first block and some-time into the break you will receive direct current stimulation (TDCS) and for some time into the break - totaling not more than 20 minutes.

You must be right handed in order to participate in this study. Also, you can only participate if you have normal vision or if you wear glasses or contact lenses that give you normal vision.

To help us determine whether you are eligible to have TDCS, you will be asked to complete a screening questionnaire. If you have any of the known risk factors, you may not be eligible to participate in this research. **Please make sure you also read the TDCS information sheet.**

Can the experiment be interrupted?

Yes. **You are free to leave the experiment at any stage**. Even if you withdraw you will be paid for the time you have spent on the study. Please be aware that any information you provide on the checklist and throughout the experiment will remain confidential. The data obtained during the experiment will also remain anonymous. You have the right to ask for your data to be removed from the study at any time during the study.

If you are uncertain about any of these points or have any questions, please feel free to ask or contact me by e-mail:

Yours sincerely,

ERN_11-0470 Approved by UoB Ethics Committee (13/11/2017) page ***1 of 1***

Appendix 1: A copy of the information sheet given to participants to read prior to taking part in the study.

The University of Birmingham
Edgbaston
Birmingham B15 2TT
United Kingdom

School of Sport, Exercise & Rehabilitation Sciences

CONSENT FORM

Title of Project: Exploring the Roles of M1 & the Cerebellum During Motor Learning

		Please Initial Each Box
1.	I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.	
3.	I understand that personal data collected during the study will be securely stored on computer and used solely for the purpose of contacting me with respect to the study or for monitoring or audit of the study by designated individuals from the University of Birmingham.	
4.	I understand that data collected during the study may be looked at by individuals from the University of Birmingham and from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
5.	I agree for data collected in this study to be given to researchers, including those working outside of the EU, to be used in other research studies. I understand that any data that leaves the school will have been anonymised so that I cannot be identified from it.	
6.	I agree for data collected in this study to be stored on computers in the University of Birmingham.	
7.	I give permission for data from this study to be used in publications. I understand that any information that would allow me to be identified will be removed from the data before publication.	
8.	I understand that this project has been reviewed by, and received ethics clearance through the SportExR Research Ethics Committee.	
9.	I understand that if I have any concerns or complaints about the study, I can contact the Principal Investigator	
10.	**By signing below, I agree to take part in the above study**	

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

Appendix 2: A copy of the consent form signed by participants prior to taking part in the study.

UNIVERSITY OF BIRMINGHAM

Motor Control & Rehabilitation Group
School of Sport, Exercise & Rehabilitation
Sciences Edgbaston, Birmingham
B15 2TT
United Kingdom
Tel:
Fax:

TDCS, TACS & TMS Safety Questionnaire

If you agree to take part in this study, please answer the following questions. The information you provide is for screening purposes only and will be kept completely confidential.

Please tick the following information where it is applies to you:

Gender: ☐ **Male** ☐ **Female**
Dominant Hand: ☐ **Right** ☐ **Left**
Fluent English Speaker: ☐ **Yes** ☐ **No**
Age (please specify) ___yrs.

	Yes	No
Have you ever suffered from any neurological or psychiatric conditions?		
If YES please give details (nature of condition, duration, current medication, etc)		
Have you ever suffered from epilepsy, febrile convulsions in infancy or had recurrent fainting spells?		
Does anyone in your immediate or distant family suffer from epilepsy?		
If YES please state your relationship to the affected family member.		
Do you suffer from migraine?		
Have you ever undergone a neurosurgical procedure (including eye surgery)?		
Do you currently have any of the following fitted to your body?		
Cochlear implant		
Heart pacemaker		
Medication Pump		
Surgical clips		

Have you ever suffered from brain injury or brain trauma?		
Do you suffer any chronic skin disorders?		
If YES (to either of the three Q above) please give details:		
Are you currently taking any un-prescribed or prescribed medication?		
If YES please give details:		
Are you currently undergoing anti-malarial treatment?		
Have you drunk more than 3 units of alcohol in the last 24 hours?		
Have you drunk alcohol already today?		
Have you had more than one cup of coffee, or other sources of caffeine, in the last hour?		
Have you used recreational drugs in the last 24 hours?		
Did you have very little sleep last night?		
Have you already participated in a TMS, TDCS or TACS experiment today?		
Have you ever participated in a TMS, TDCS or TACS experiment before?		
If YES please outline when:		

I confirm that the above information is accurate to the best of my knowledge.

Print Name:	Date:
Signature:	
This form has been verified by (Staff only):	Date:
Print Name:	
Signature:	

Appendix 3: A copy of the safety form/questionnaire signed by participants prior to taking part in the study.

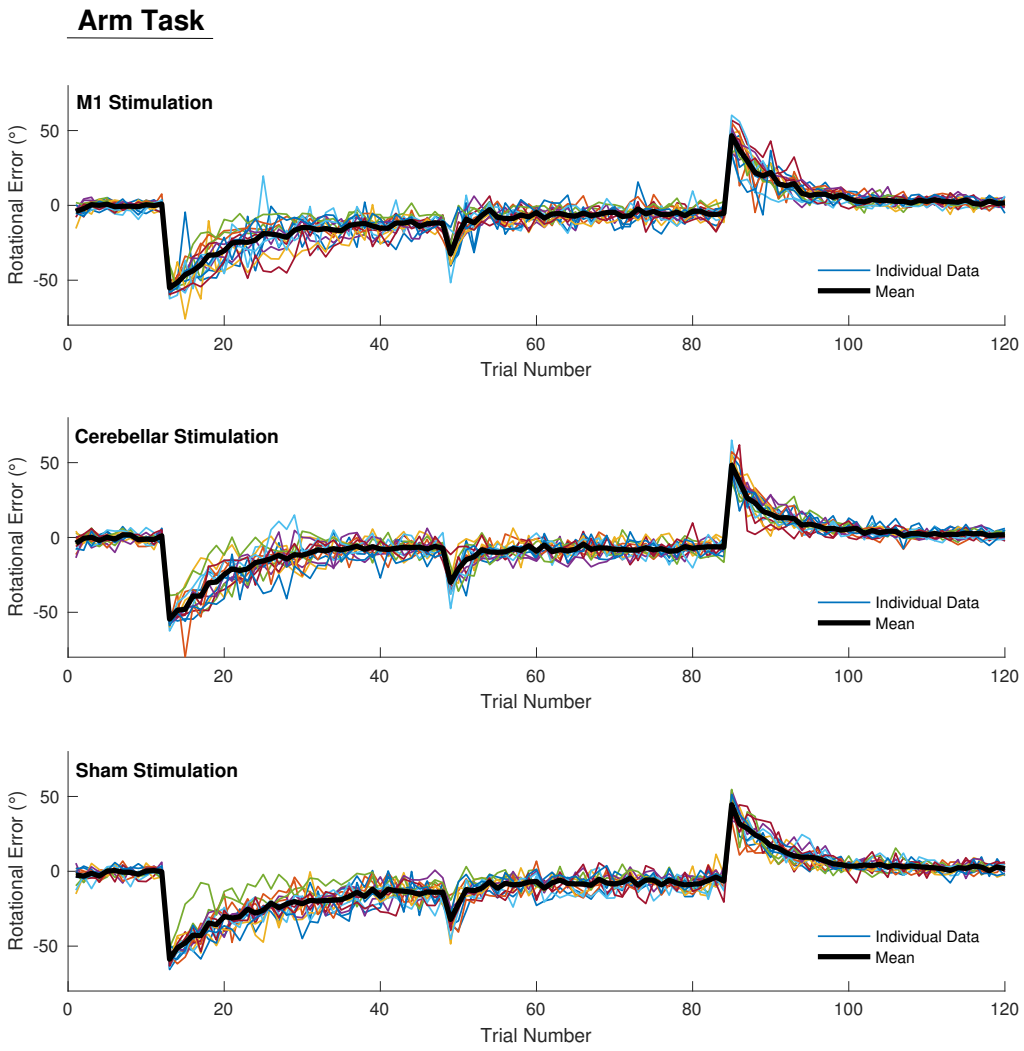
On the scale below, please rate your comfort level during stimulation. 1 - being 'No Discomfort' and 10 - being 'Very High Discomfort'.

1 2 3 4 5 6 7 8 9 10

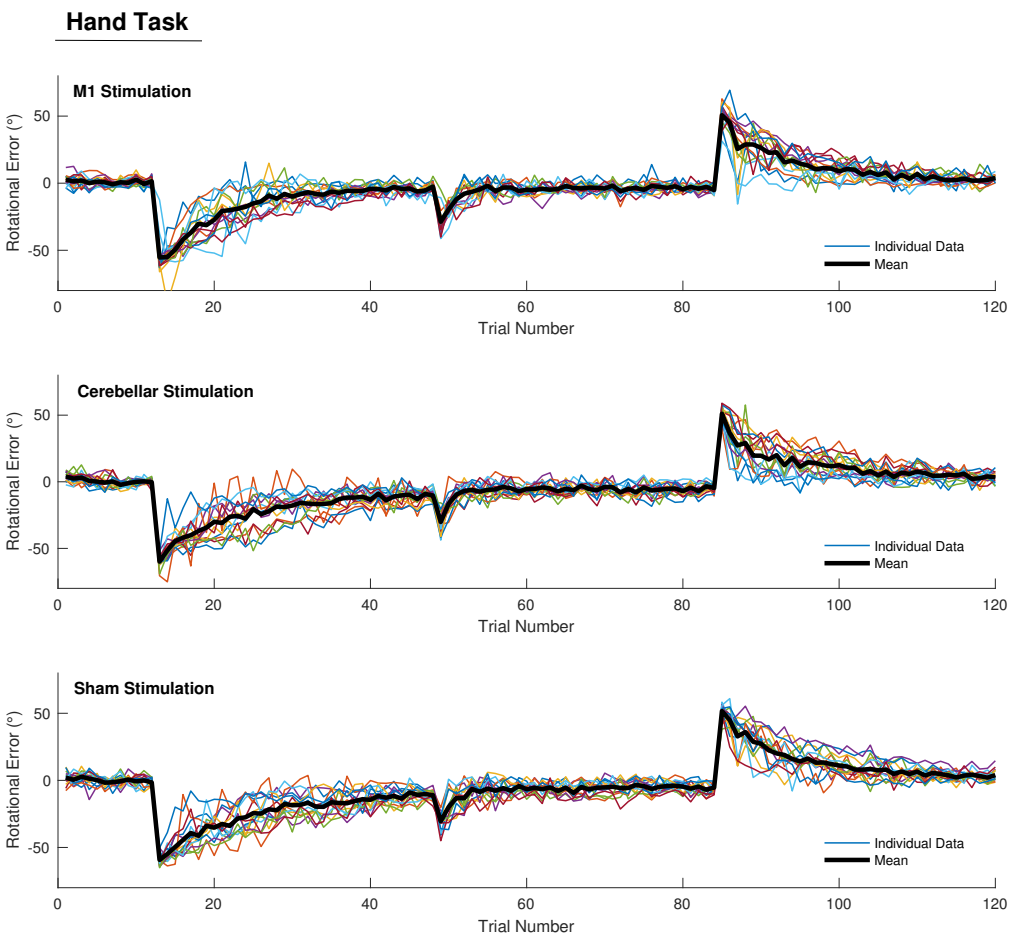
On the scale below, please rate to what extent you believed you received real TDCS (i.e. Active stimulation vs Placebo stimulation). 1 - being 'I don't believe I received real stimulation at all' and 10 – being 'I am 100% sure I received real stimulation'.

1 2 3 4 5 6 7 8 9 10

Appendix 4: A copy of the VAS questions given to participants after they received stimulation. Participants were asked to circle the most appropriate number.



Appendix 5: Raw individual data vs Mean for the three stimulation groups during the Arm Task.



Appendix 6: Raw individual data vs Mean for the three stimulation groups during the Hand Task.